FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ JUNE 1993

HEALY'S FAREWELL

On June 30, two years after she became the first woman ever to head the U.S. government's premier biomedical institution, Bernadine Healy leaves NIH. But many of the initiatives she has launched will continue to flourish long after Healy leaves the institution.

During her term, Healy put women's health issues high on the NIH agenda and launched the Women's Health Initiative, a 14-year, $625 million clinical megastudy of 150,000 women to examine the causes of death and disability in women as they age. Healy added another feather to her cap when she recruited geneticist Francis Collins to head the Human Genome Project and to set up a new intramural program in human genetics. Collins, in turn, is recruiting some of the best and brightest geneticists to NIH. Healy also led an unprecedented effort to develop an NIH Strategic Plan. Called *Investment for Humanity*, the plan is a loose framework to guide scientists nationwide as they plan for the future of biomedical research. As part of this endeavor, Healy brought together more than 2,000 representatives of the scientific community to define priorities and develop a vision for NIH.

As a farewell tribute to Healy, *The Catalyst* is reprinting the introduction to the NIH Strategic Plan (*see page 4*). We also asked Healy to answer three questions. She obliged. Her answers to our questions are published on page 5. — *S.K.* ■

REPORT OF THE TASK FORCE ON THE STATUS OF NIH INTRAMURAL WOMEN SCIENTISTS

Published below, for your review and comment, are the recommendations of the Task Force on the Status of Women at NIH. The Scientific Directors (SDs) are working to implement new policies to address all the issues raised by the Task Force. The Women Scientist Advisors to SDs have been appointed and are active. A list of these advisors is available from *The Catalyst* office and will be published in the next issue. Three of the Task Force's seven recommendations — establishing a uniform tenure plan, a uniform promotion plan, and a family-leave flextime plan — were omitted here either because they have already been established or are undergoing further analyses by the Task Force. Write your comments on the FAX-BACK response sheet on page 20 and fax or mail it to us by August 1. ■

Executive Summary

Background and Goals

The Task Force on the Status of NIH Intramural Women Scientists, composed of tenured and non-tenured scientists and individuals from the Office of the Director at NIH, met for the first time in November 1991 to

- assess the career development and status of intramural women scientists at NIH by gathering and analyzing data on their recruitment, retention, compensation, and reentry into the work force;
- determine whether there are real (or perceived) impediments to career development of women scientists at NIH; and
- recommend to NIH's Deputy Director for Intramural Research and its Director administrative and structural changes to correct any identified problems, and thereby to enhance the career development and status of NIH women scientists.

Four widely advertised public forums were held on tenure, pay, and promotion; job sharing; mentoring, leadership, and visibility; and family leave and day care. The forums provided opportunities for NIH scientists to bring a variety of concerns to the attention of the task force.

INEQUITIES EXIST FOR NIH INTRAMURAL WOMEN SCIENTISTS WITH REGARD TO PAY, TENURE, PROMOTION, AND VISIBILITY.

Findings

The task force's findings include the following:

- Underrepresentation of women scientists at NIH does not occur in the pool of postdoctoral trainees: women average 29.5% of the pool over the past 10 years, with a recent increase in 1990 and 1991 to 35.3%. These percentages closely mirror the percentage of women completing Ph.D. training in life sciences (35.1%) and women in M.D. residency programs (29.5%).
- Disparities and inequities exist for NIH intramural women scientists with regard to pay, tenure, promotion, and visibility.

continued on page 17.

NEW POLICIES, PROGRAMS TO ENHANCE QUALITY OF SCIENTIFIC LIFE

Lance A. Liotta

Many developments over the past several months will significantly improve the quality of scientific life and enhance career development and creative scientific opportunities for intramural NIH scientists.

- NIH is implementing the new tenure-track, "stop-the-clock," "extend-the-clock," and family leave policies over the next several months. The Scientific Directors (SDs) are working to implement new policies to address all the issues raised by the Task Force on the Status of Women Scientists, published in this issue of *The Catalyst* so that you can comment on them before they are fully implemented. We have already appointed the Women Scientist Advisors to the Scientific Directors.
- Early this month, the SDs unanimously accepted a proposal by John McLachlan, SD of NIEHS, that would remove a significant delay in scientific promotions. When evaluating a candidate for promotion, laboratory chiefs will no longer be required to wait for an additional review by the Board of Scientific Counselors if the candidate's last review was positive and the promotion is warranted by recent scientific accomplishments.
- FAX-BACK responses on the parking exemption for families who need to drop their children off at day care or school and on the low-interest or no-interest tuition loans for employees were positive. We are now developing implementation strategies for these ideas.
- The NIH revitalization bill signed this month by President Bill Clinton establishes the National Foundation for Biomedical Research — a nonprofit corporation to support the NIH mission "and to advance collaboration with biomedical researchers from universities, industry and nonprofit organizations." The new foundation is authorized to incorporate the Foundation for Advanced Education in the Sciences (FAES) and provides a flexible way to administer endowed positions, fellowships, and grants to NIH research personnel. Specifically, "such fellowships and grants may include stipends, travel, health insurance benefits and other appropriate expenses." The foundation will support meetings, conferences, book selling, courses, and science education at all levels. Further details will be provided in a future issue of *The Catalyst*.
- The revitalization bill also expands programs for postdoctoral-loan repayments for NIH scientists beyond those already approved for AIDS-related research. The new loan-repayment authorization now allows loan repayment through "research training, research, or teaching that is health related." The program will be open to all NIH Scientists, and in addition, provisions have been made to stimulate "the recruitment of women and individuals from disadvantaged backgrounds (including racial and ethnic minorities) into the fields of biomedical and behavioral research." Further details will be provided in a future issue of *The Catalyst*.

WE HAVE ALREADY APPOINTED THE WOMEN SCIENTIST ADVISORS TO THE SCIENTIFIC DIRECTORS.

- The Institute Directors have endorsed an improved system for the cost management of the Clinical Center (CC) that uses prospective planning, basal costs for clinical support services, and assessments based on space utilization rather than numbers of beds used in research. John Gallin, SD of NIAID, will summarize the new approach in the next issue of *The Catalyst*.
- We have launched a multifront attack on the costs, complications, and some undesirable consequences of technology transfer. This month's FAX-BACK page includes a question on this topic. We established the Technology Transfer Policy Board (TTPB) to address concerns raised about material transfer agreements (MTAs), cooperative research and development agreements (CRADAs), and patents. Subcommittees of the TTPB will review tech-transfer training, CRADAs, patent and royalty costs, and management issues. At the first TTPB meeting, John Gallin presented a Macintosh-based, "paperless" system for filing invention reports and tracking the status of patent filings. This module, previously approved by the SDs, is now being field-tested. Reid Adler, Director of the Division of Technology Transfer, presented the concept of having uniform biological (Treaty) MTAs with academic institutions and discussed the recent agreement between NIH and the American Type Culture Collection (ATCC) in Rockville, MD, that should lead to a paperless material-transfer system and greatly reduce the burden of time-consuming mailing of reagents by intramural scientists. "Letter of intent" CRADAs, presented by Tom Mays to the CRADA Subcommittee, chaired by Dinah Singer, will speed intitiation of new CRADAs. "Letter of intent" CRADAs will also allow scientists to receive reagents, such as experimental drugs, from companies unwilling to provide these reagents under a government MTA. The "letter of intent" CRADA allows a company to retain the right to negotiate an exclusive or nonexclusive license for inventions by NIH scientists using the company's reagents.

Finally, our FAX-BACK feature has been a great hit! Thank you for participating in this ongoing "electronic town meeting." We receive an average of three to five suggestions and opinions daily — suggestions that are extremely valuable in policy development. Your responses to all five questions in the April issue of *The Catalyst* were mostly positive and supportive of the issues that were proposed — the tenure-track policy, the interinstitute faculties, the carpool-parking exemption for parents, the low- or no-interest tuition loan program and *The Catalyst* itself. On page 3 are some excerpts from your comments. Keep them coming! Your opinion can make a difference.

Lance A. Liotta, Deputy Director for Intramural Research

FAX-BACK Feedback

Below is a sample of the FAX-BACK comments we received for each topic raised in the April issue.

The tenure track policy

"Reasonable and long overdue. Hopefully, it will elevate the quality of tenured scientists [at] NIH by involving a review committee above the laboratory level." — *A.G. Hinnebusch, NICHD.*

"Implicit in the categorization of investigators as 'senior investigators' or 'staff scientists' is a two-tiered system in which collaborative scientists would inevitably come to be perceived as second-class citizens of the scientific community. I am particularly concerned that such a system could introduce, over the long term, bias against 'basic sciences' such as chemistry or spectroscopy, whose functions might be regarded as ancillary to biomedicine as a whole, and whose practitioners would thus disproportionately be candidates for the less prestigious 'staff scientist' positions." — *J.M. Sayer, NIDDK.*

On the interinstitute advisory faculties

"Potentially a very important means [of] communication amongst our intramural programs." — *G.H. Smith, NCI*

"Basically a sound idea. But I fear it would create a second layer of bureaucratic complexity." — *J.A. Hanover, NIDDK.*

On the car-pool parking exemption

"Good idea! Parents with young children need all the help they can get!." — *M. Daniels, NHLBI.*

"I think it is a great idea and is necessary to make NIH 'family-friendly.' Let's do it." — *R.M. Long, NIGMS.*

"Great idea, but be very careful it is not abused. I am a carpool member and am aggravated by the people who try to get around the system. Thanks for the recent crackdown, by the way." — *R.K. Ribaudo, NIAID*

On the low-interest or no-interest tuition-loan program

"Great idea; might be critical for retention." — *R.H. Wiltrout, NCI, FCRDC*

"Absolutely! With no financial criterion, so it would be a benefit." — *N. Salem, Jr., NIAAA.*

"Extremely good idea; would be a major positive factor in retention." — *J.A. Beutler, FCRDC, NCI.*

"An incentive to both progress and stay at NIH." — *Anonymous.*

On the newsletter

"The expanded science is very good. More of this." — *Anonymous.*

"Focus more on administrative issues ... recently tenured, and expand the opinion polls — *J. Grafman, NINDS.*

"Interesting and informative." — *M.A. Crawford, NEI*

"Keep it coming." — *R.M. Long, NIGMS.* ■

"Fingerprints," a play written by students at Northeast High School in Pasadena, MD, won the 1993 playwriting competition organized by the Office of Education. The winners performed at the Masur Auditorium last month. ■

Letters to the Editor

The Intramural Clinical Research Program

Recently, the clinical and scientific directors jointly addressed concerns about the health of intramural clinical research. The concerns are related to the decrease in in-patient census figures and to the small number of newly tenured investigators engaged in substantial clinical studies. It has also been claimed that the clinical community is under appreciated by the scientific directors because they prefer reductionist research, or want to save money, or both.

The discussions raised some doubts about the validity of both the basic concern (i.e., that clinical research is foundering) and about the reasons behind the phenomenon (to the extent that it is a real one). Because even erroneous perceptions can destroy morale and be self-fulfilling, they need to be dealt with. Here I outline my own attitudes about this issue.

I reserve the term "clinical research" (as opposed to "health-related research") for investigations carried out on humans (and not simply on samples of their tissue), recognizing that such distinctions can never be absolute. As thus defined, clinical research is likely to be sharply constrained by ethical considerations, to be expensive, to be lengthy, to have to eschew desirable controls, and to require extensive collaborations with individuals who contribute sophisticated but nevertheless service functions.

Despite these special characteristics, one can ask of clinical research, as of all other research: Is it interesting, innovative, and incisive and does it ask important questions, or is it dull, derivative and plodding? Will a favorable end-result yield only a modest modification of existent therapy, or could it lead to a truly novel therapy, prevention of disease, or substantial new insights into normal or deranged physiology?

Some patients are treated at NIH to fulfill training requirements for our clinical associates, and some more pedestrian therapeutic protocols recruit patients who contribute samples for more compelling research. But we should minimize the use of our limited research funds for such purposes. To ensure that we are supporting the highest-quality research, we should purge out-patient rosters of patients who are not required for present or future protocols, and we should not dispense medications that can be purchased otherwise.

We should assess whether there are institutional impediments to pursuing clinical research and whether we are failing to communicate adequately our appreciation of such research, and we should work together to correct such deficiencies. However, we all know that clinical investigations are extraordinarily difficult to pursue outside of Bethesda. That environment may limit the pool of young investigators who are willing to commit themselves to clinical investigations. In such an extramural environment, we may not be able to achieve intramurally as much as we may wish.

Having sat on the Board of Scientific Directors for quite a few years, I believe that most of my colleagues agree with my sentiments and that the clinical community has underestimated the extent to which the scientific directors share their goals and value their efforts.

H. Metzger, *Sci. Dir., NIAMS*

Investment for Humanity

by Bernadine Healy

". . . to intervene, even briefly, between our fellow creatures and their suffering or death, is our most authentic answer to the question of our humanity."

—Howard Sackler, American playwright

The National Institutes of Health (NIH) was established more than a century ago to improve and safeguard the health of every American.

Today, NIH continues to pursue science for the sake of each man, woman, and child in the United States, reflecting the central tenet of our democratic society: the belief in the value and sanctity of the individual. Science for the sake of the citizen is an idea that has grown up with America. Thus, it is no accident that the United States, the world's greatest democracy, has created the world's greatest biomedical research establishment, dedicated to serving not the state, but the individuals who make up the state.

The fruits of NIH's medical research have proven to be among our Nation's greatest achievements, saving countless lives and profoundly improving the human condition. NIH has translated the American public's investment into far-reaching biomedical discoveries and a wealth of scientific knowledge that benefit all of humanity.

NIH is a large, complex organization. It is, in fact, a nationwide republic of science, composed of some 50,000 individual researchers working at 1,700 institutions across the country. NIH's intellectual capital base and scientific resources are devoted to addressing the most challenging, urgent public health and biomedical questions of our time. The growing complexity of these challenges — ranging from reducing the suffering from heart disease and cancer to finding a cure for AIDS — coupled with the urgent need to manage prudently the U.S. taxpayers' $10 billion investment in NIH, requires that we think very carefully about our future.

That is precisely what occurred as we embarked upon our strategic planning effort. The leadership of NIH along with some 2,000 representatives of the scientific community — from our intramural community and from NIH-supported institutions nationwide — participate in this process. The plan is a vision, not a blueprint; it is a framework, not a manual of operations; it is a beginning, not an end. It defines an NIH flexible enough to respond to society's changing health care needs and dynamic enough to open ever more promising frontiers of fundamental research. Although a new undertaking for NIH, the Strategic Plan does not sever ties with the past. Rather, it builds on past accomplishments, organizational strengths, and approaches of proven value. This document also affirms our commitment to the individuals who are the NIH: they are the source of our creative advances, primarily through their insights, initiatives, and individual talent.

Investment for Humanity is predicated upon the need to create an environment that promotes creativity on the part of individual scientists. The pursuit of research opportunities that are closely aligned with our Nation's health goals and our citizens' individual needs is also central to our plan. By focusing NIH's organizational thinking, the Strategic Plan articulates how our community defines its priorities for investment.

Science for the sake of the citizen is an idea that has grown up with America.

The Strategic Plan starts with our statement of mission — *science in pursuit of knowledge to improve human health*. All that follows derives from and relates to that central guiding mission. Woven throughout this plan is a firm recognition of 1) a commitment to basic and clinical research as the means of expanding our knowledge base; 2) the importance of nurturing and sustaining a robust and varied human capital base; and 3) the need for sophisticated infrastructure to accomplish both. Although the specific initiatives may change as science and the needs of society change, NIH's fundamental mission and purpose will remain immutable.

There are no greater perils to our people and the promise of our Nation than the scourges of cancer, heart disease, drug and alcohol abuse, mental illness, debilitating diseases of the elderly, and new emerging threats such as AIDS and drug-resistant tuberculosis. Investing in NIH is the single greatest action our Nation can take to overcome these and other devastating illnesses. Indeed, the history of NIH and its record of achievement provide compelling evidence that no other public investment has yielded a greater return, over a longer period of time, for every U.S. citizen.

The benefits of that investment extend also to our Nation's economy. The biotechnology, bioengineering, and pharmaceutical industries (and related life-science-based corporations) are increasingly important to improving the Nation's economy — creating new jobs, technologies, products, and services. In many regions of the country, biomedical science is a great catalyst for the creation of skilled, high-level jobs and is responsible for considerable economic productivity. NIH is the engine that drives this emerging "bioeconomy": an economy that will lead to better health, lower health care costs, and sustained economic growth. The NIH Strategic Plan will help ensure that our Nation remains at the forefront of the burgeoning economy.

Investment for Humanity pledges the NIH community to address the opportunities, challenges, and needs for the future with vigor, dedication, and integrity. In turn, it also calls for a reciprocal commitment from this Nation's citizens and their elected representatives, not only to sustain, but also to enhance the strength and vitality of this unique institution — this republic of science — they have created and nurtured over many years. For NIH to fulfill its mission of pursuing science for the sake of each citizen, our vital enterprise must be a national priority. ■

NO REGRETS: HEALY REFLECTS ON HER TERM AT THE HELM

As she prepared to leave office we asked Bernadine Healy to answer three questions. Below are are our questions and her answers.

Q: If you were asked to advise members of the search committee that is selecting the new Director for NIH, what would you tell them, and what advice would you have for the next NIH Director?

A: I would start with reminding the committee of the importance of our mission statement — we are here to "pursue new, fundamental basic knowledge to extend healthy life and reduce the burdens of illness." This statement reflects the heart and soul of our institution and underscores our paramount concern for public health. NIH has consistently ranked among the most respected of governmental agencies, and we must strive to keep it that way through outstanding leadership and direction. This means selecting a director who is committed to responding to the public's expectations for NIH; focusing attention on the social, legal, and ethical issues inherent in research; and providing close scrutiny to our management of substantial public resources. It means, in short, designating a good and accountable steward who can direct the institution toward excellence in every area.

The most essential advice for my successor would go back to what I said in my confirmation statement to the Senate: *"The NIH is a national treasure — the fruits of NIH's medical research have proven to be among our nation's greatest achievements, saving countless lives and profoundly improving the human condition."* You should be deeply honored to serve this great institution and will have the privilege of working with superb deputy directors, institute directors, and staff within the Office of the Director. This superior leadership will provide perpetual support to you, and ensure NIH's success throughout your tenure.

Q: For what three accomplishments at NIH would you like to be remembered, and do you have any regrets?

A: Regarding my accomplishments — this is not for me to judge, but for others and history to determine. However, there are areas in which we have made strides and that give me a personal sense of pride.

- *Strategic Plan* — The Strategic Plan for NIH is a framework to assist our nationwide network of scientists in planning for the future. Over 2,000 representatives of the scientific community participated in the process to define priorities that directly relate to NIH's mission — "science in pursuit of knowledge to improve human health." Strategic planning is about helping to shape the NIH of tomorrow in the face of a changing world. If NIH's Strategic Plan has a favorable impact on resources, it will do so only because it offers a compelling vision that inspires action, entices investment, and presents NIH to the public as a noble enterprise worthy of advancement and essential to our nation's future.

- *Women's Health Initiative* — This landmark prevention trial is well on its way. It will address cardiovascular disease, cancer, and osteoporosis — the leading causes of death, disability, and frailty among post-menopausal women. The Women's Health Initiative will affect millions of women and is expected to provide all women with scientifically valid data and information to use in making informed decisions about their health.

- *Human Genome Program* — The expansion of the program through its newly established Division of Intramural Research will focus on technologies for fighting disease genes and developing diagnostics and gene therapies. Under Francis Collins' leadership, NIH has acquired world-class talent and experience in human genetics research.

- *Revitalization of the Intramural Program* — I may not have succeeded with the parking problem, but we have seen a renewed vigor and interest in the Intramural Research Program at NIH. Additionally, the master plan for the NIH campus is in the process of development. This is a significant endeavor because it hasn't been updated since the 1970s.

Regarding regrets — I don't look back. I have been privileged to work with distinguished scientists and administrators here at NIH, and I know they will continue to move NIH forward.

Q: What do you predict will be the most serious challenges for the Intramural Research Program in the years ahead?

A: The Intramural Research Program is the flagship of NIH, offering unique opportunities to do high-risk, long-term research in an environment that is intellectually alive and relevant. The fate of NIH as a whole is linked to the success of its Intramural Research Program. Intramural scientists chafe under restrictions limiting them from participating fully in professional societies, from planning scientific meetings, from garnering honoraria, from writing or speaking about federally funded research, and from purchasing equipment without a *Federal Register* notice. Probably the biggest and most serious challenge for the years ahead is expanding the talent base of intramural scientists through increased funding and training programs and expanding tenure-track scientific positions and Senior Executive and Scientific Services positions. We must also unburden scientists from restraints on their salaries and honoraria that were never intended for them in the first place. Efforts in these areas must be relentless. Lance Liotta is extremely determined to pursue his beliefs and is a strong advocate of what is *best* for NIH. ■

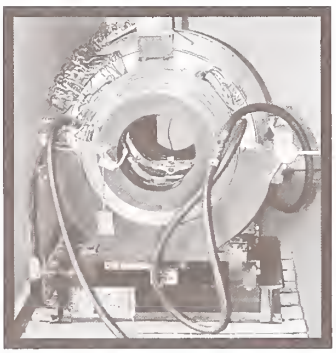
In the Next Issue. . .

The Fix-It Folks: NCRR's Biomedical Engineers Tailor Solutions to Technology Problems

by Seema Kumar

The assorted group of nearly 90 engineers, physical scientists, mathematicians, instrument makers, and technicians that make up NIH's Biomedical Engineering and Instrumentation Program (BEIP) are alike in one respect, says Murray Eden, who has headed NCRR's BEIP for nearly 20 years. "We are problem solvers, and no intramural scientist's problem is too big or small for us to handle," says Eden.

BEIP's problem-solvers have built plastic eggs in which to ship embryos of endangered whooping cranes, solved differential equations in order to understand the pharmacokinetics of drug delivery, built one-of-a-kind instruments, and fixed countless broken microscopes.



BEIP engineers built the first and only spherical MRI magnet.

"If an NIH investigator has a problem and needs an instrument made that [he or she] can't buy in the market, then we will develop it, whether it is going to be unique or whether [there are] going to be 10,000 more made like it," says Eden. "Our primary concern is [to meet] the need of the intramural investigator."

Each year, BEIP personnel assist researchers with more than 200 intramural projects, designing and producing advanced instrumentation, models, and techniques that are not commercially available. In addition, BEIP personnel typically respond to about 1,500 or so requests for fabrication or major modification of laboratory equipment, and nearly 10,000 requests for repairs or minor modifications of scientific equipment.

Because BEIP undertakes projects that are often directed at solving specific problems of intramural investigators, and because the instrumentation is not available elsewhere, most of what BEIP turns out is unique. This has resulted in many BEIP firsts.

Take, for example, the only spherical magnetic resonance imaging (MRI) magnet ever built. This unit, which now decorates the lobby of the third floor of Building 13, was built in-house to study small animals and neonates and to perfect a technique called shimming, now used world-wide to stabilize magnetic fields in MRI scanners. BEIP also blazed the trail in the 1970s with the first fiber-optic pH probe. A variation of this sensor is now used by NOAA to measure pH thousands of meters below the ocean surface. Another BEIP first: the video-rate confocal microscope developed in 1989 by Seth Goldstein. The confocal microscope has no moving parts and produces section-like images of tissue in real time. In 1980 Goldstein and former BEIP engineer Dan Shook also perfected the everting toposcopic catheter, used to maneuver virtually frictionlessly through narrow, tortuous blood vessels. The catheter is on display at NIH's DeWitt Stetten Museum. Also on display is a system developed by BEIP's Thomas Clem that dramatically reduced the time and labor involved in reading the enzyme linked immunosorbent assay (ELISA). After making about a dozen ELISA machines for intramural scientists' use, BEIP relinquished all patent rights and gave the technology to the world; all commercial, automated versions of ELISA readers are based on BEIP's original invention.

The introduction of cooperative research and development agreements (CRADAs) has not changed BEIP's basic mission too much, says Eden. Although BEIP personnel are encouraged to patent, "we don't put too much stress on that," says Eden. "Our main goal is to solve instrumentation problems of intramural scientists."

Eden says that in the next few years, BEIP plans to move into the biomaterials field. "We are interested in collaborating with institutes to study and develop materials for a variety of diagnostic and therapeutic purposes," says Eden. These include methods to encapsulate tissues, such as pancreatic beta cells, to protect them from the immune system but still allow them to be nourished by the body and to produce insulin. Eden plans to develop other hybrid materials — part synthetic and part biological — for use in prosthetics that will integrate with the rest of the body.

At BEIP's fabrication shops, skilled workers design and fabricate special instruments for NIH researchers.

In the meantime, BEIP's Scientific Equipment Services (SES), composed of several fabrication and repair facilities and the Scientific Equipment Resources Program (SERP), upholds BEIP's problem-solving tradition in repair, service, rental, and sale of laboratory and clinical equipment. Its fabrication shops, staffed by a skilled cadre of instrument makers, technicians, welders, and glass blowers design and fabricate a wide variety of specialized instrumentation for NIH researchers. Like the products of their engineering colleagues, what SES staff turn out is often one-of-a-kind — prototypes that have been adopted and duplicated by other research institutions.

But "the most unique thing about the shops is the people who work in these units," says Howard Metz, who heads SES. "The skills and the working relationships they have developed with the scientists allow us to offer a service that is unique to NIH."

"We have considerable talent and valuable experience in a small package," says Jim Sullivan of the Precision Instruments Unit. Sullivan says BEIP personnel save time because they don't have to look outside for advice. "We have all sorts of skills in the crafts and in the sciences right here at Building 13."

A BEIP Sampler

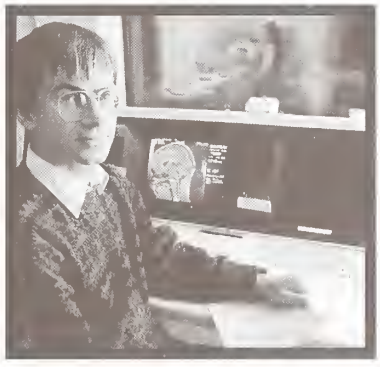
Fast, 3-D Functional MRI Method Allows Better Brain Mapping

Functional mapping of the human brain — charting regions that are activated by specific tasks or stimuli — is a hot research area at NIH. In fact, functional mapping is beginning to monopolize the magnetic resonance (MR) scanner at NIH's in vivo NMR Research Center, according to BEIP's Chrit Moonen, a biophysicist who manages the center.

Until recently, functional mapping relied heavily on positron emission tomography (PET). Although MR techniques provided advantages over PET, state-of-the-art NMR techniques for anatomy were inadequate for functional mapping. Techniques that were sensitive to physiology provided only 2-D images, and those that gave 3-D information did

so by sacrificing sensitivity. Mapping brain function with MR requires sensitivity to local physiological parameters such as blood flow and metabolic activity. But it also calls for excellent anatomic detail in three dimensions.

Responding to the need for a better technique, Moonen and his team, together with the Laboratory of Diagnostic Radiology Research, developed a fast, 3-D, functional MRI method just two months ago that can be used with conventional MRI scanners. The method, called echo-shifted FLASH, is an improvement over other fast NMR technologies that are now being snapped up by brain cartographers across the country. Echo-shifted FLASH goes a step beyond fast NMR and offers dramatically increased sensitivity to dynamic physiological effects, permitting researchers to accurately map the function.



BEIP's Chrit Moonen manages the NIH in vivo NMR Research Center.

"We expect a lot from this technique," says Moonen. "Our basic development is done, and the time is ripe" to put this technique into the "hands of neuroscientists for further applications." A patent on this technique is pending.

Several NIH laboratories from various institutes are already lining up to use echo-shifted FLASH. Daniel Weinberger and his team at NIMH have been heavily involved in the testing stage of this new technique for their studies of people with schizophrenia. Other investigators at NINDS, NIMH, and NIA who have large, ongoing research programs that involve functional MRI may also benefit from the new technique, says Moonen.

Anti-Cancer Drugs: We Deliver Better with Less

Robert Dedrick, Paul Morrison, Cynthia Sung and their NINDS collaborators could predict that a new anti-cancer drug, Tfn-107, would be difficult to administer by conventional approaches. From the thermodynamics and kinetics of Tfn-107, the researchers could tell that getting concentrations of it high enough in the brain to kill cancer cells was going to be difficult.

The problem, says Dedrick, is that Tfn-107 is a large molecule (molecular weight, 130,000). Many drugs, and especially large molecules, have difficulty overcoming the blood-brain barrier and reaching brain sites via the bloodstream. Dedrick predicted that if Tfn-107 was injected intravenously, only a fraction of the initial dose would reach the brain. To attain therapeutic concentrations, researchers would have to use doses that could be toxic to normal organs.

"This very low rate of transport between the brain and the blood [would] make the ideal setting for some sort of device that releases the drug [directly to the brain] by diffusion," says Dedrick. Regional drug-delivery methods that use a variety of slow-release or biodegradable polymer implants to deliver anti-cancer drugs directly to the tumor site are already used to treat certain types of brain cancers.

Unfortunately, according to Dedrick's calculations, Tfn-107 is such a large molecule that even if it were placed directly in the brain, simple diffusion would not spread the drug quickly or widely enough to kill cancer cells in adjacent tissue.

Dedrick and his team calculated that their collaborators would have better success in treating brain cancer with Tfn-107 if they infuse the drug under pressure directly into the tumor or surrounding tissue. A mathematical model of this process showed that the drug would be carried by bulk flow, resulting in higher concentrations as well as a more uniform distribution over large tissue volumes.

Collaborators Edward Oldfield, Douglas Laske, and colleagues at NINDS' Surgical Neurology Branch have used this approach clinically and now are close to completing a phase I clinical trial of Tfn-107 in patients with glioblastoma multiforme and other solid tumors of the brain. The researchers have determined the maximum tolerated dose for infusing the agent and are excited about the clinical response of several patients.

BEIP's Annalie Burke (left) and Howard Metz (right). Burke oversees rental and sales of laboratory and clinical equipment.

Fiber-Optic pH Probe: Working Its Way through the System

John Peterson, a BEIP scientist, and Eden Netto, a doctoral student from the University of Campinas, Brazil, are developing a fiber-optic pH sensor and related instrumentation that could be used to measure and monitor pH in the stomach and duodenum.

The instrument could help research, diagnose, and evaluate acid-related disorders of the upper gastrointestinal tract such as duodenal and peptic ulcers and gastritis. The probe could also be used to study the influence of diet and antisecretory drugs on gastric disorders, says Peterson. "The sensor makes use of the latest technology and, if developed, will be the first fiber-optic sensor to measure gastric pH in vivo," says Peterson. More importantly, says Peterson, it offers many advantages over existing methods for in vivo pH measurements.

Currently, researchers measure pH in the stomach and duodenum by using electrodes that are uncomfortable, cumbersome, and prone to problems from electrode coatings and electrical safety hazards. The fiber-optic probe is smaller (0.5-1 mm thick), safer, and more reliable, says Peterson. In addition, patients could wear the pH- monitoring system for up to 24 hours — a typical period over which gastric changes are measured.

The instrument can measure a pH range of 0-10, with an accuracy of 0.1 pH unit. The normal pH in the stomach ranges from 1 to 4, but in patients with gastric problems, the pH goes up to 7. The fiber-optic sensors measure pH the old-fashioned way — by detecting changes in colors of dyes that vary with pH. In 1978, Peterson and Seth Goldstein developed the world's first fiber-optic pH probe. The single-dye sensor measures the pH in working heart muscle and measured a physiological pH of 7.4.

Peterson and Netto aimed to improve this original sensor by increasing the *continued on page 8.*

NIH INSTRUMENTATION
continued from page 7.

range of measurement to six or more units — necessary to measure pH variation in the stomach. But, "a broad range pH measurement is a considerably more difficult technical problem because it involves using multiple indicators (dyes)," says Peterson. The newly designed probe achieves its nine-unit range with two dyes.

Netto has been working in Peterson's laboratory for the past two years to identify suitable dyes and instrumentation to incorporate into the optical fiber. "The next step is to try to measure pH in gastric juices in vitro and compare pH as measured by conventional pH meters and by the fiber-optic probe," says Netto, who hopes to test the probe in vivo before the end of this year.

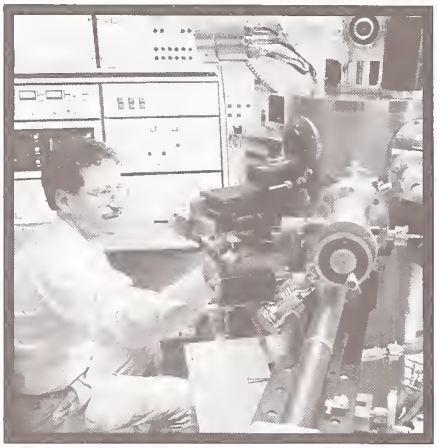
"We are fast approaching the point of building an instrument," says Peterson. "We have done all the preliminary work and would like to build an instrument that can be used clinically." Peterson hopes to find intramural collaborators who might be able to use this new instrument.

Detecting Low Calcium Concentrations in Organelles

Physicist Richard Leapman and his BEIP colleagues are "trying to fill a technological niche between molecular biology and cell biology." Using an analytical scanning transmission electron microscope (STEM), which provides quantitative information about biological structures, Leapman and his team study ion concentrations in subcellular organelles and molecular weight distributions in macromolecular assemblies. The researchers use rapid-freezing and low-temperature techniques to preserve these structures in a close-to-living state.

Recently, Leapman and his colleagues discovered that by using a technique called electron energy loss spectroscopy, or EELS, with STEM, they can map extremely low concentrations of calcium in thin sections of rapidly-frozen tissue, achieving a sensitivity significantly higher than that achieved by X-ray spectroscopy, the currently used method to measure calcium concentrations in organelles.

"There is no better method for measuring total calcium in such small structures," says Leapman. "Attaining high spatial resolution with X-ray spectroscopy has been difficult without compromising sensitivity." Leapman says the new method provides a resolution and sensitivity that is better than "anybody has ever achieved before." The technique is complementary to fluorescent light optical methods which measure free (rather than total) calcium concentrations at lower spatial resolution.



Richard Leapman uses the BEIP field-emission scanning transmission electron microscope to map structure amd composition of cells and macromolecules at high spatial resolution.

Calcium, an intracellular second messenger for many cellular functions, is harder to detect than other biologically important elements such as sodium, potassium, or chloride because physiological concentrations of calcium typically are in the sub-millimolar range — typically about 40 calcium atoms in an organelle with a diameter of 50 nm. A 10% change in calcium concentration would correspond to a variation of only few atoms in an organelle. Using the new technique, Leapman and collaborators Thomas Reese and Brian Andrews in the Laboratory of Neurobiology, NINDS, were able to detect changes of just a few dozen calcium atoms in synaptic vesicles and segments of endoplasmic reticulum in cerebellar cortex. Their results from neuronal dendrites in mouse cerebellar cortex support a growing consensus that the endoplasmic reticulum, not the mitochondrion, is the major calcium-regulating organelle in neurons and, probably, most other cells.

BEIP engineers played several key roles in the STEM study, including adapting the EELS technique for the analysis of biological systems and the development of cryo-techniques for the instrument. Applying STEM to biological materials also meant developing a system that could produce images using very-low-electron-beam doses that do not damage the delicate samples.

BEIP's STEM is one of three such instruments in the world that are being used for biological research. "None of the techniques [we develop] are standard," says Leapman. "We can't just simply use a recipe to solve a problem ... everything has to be custom- made for each problem, and this is true for most problems that come here." ■

NCRR Requests Input for its Own Strategic Plan

Judith Vaitukaitis, the newly appointed director of NCRR, wants your views on the technology, resources and services provided by NCRR. Vaitukaitis says the information will help NCRR draft its strategic plan to improve and develop the center's contribution to intramural research. Your response will be analyzed and presented to panels convened later this year to develop specific objectives for the NCRR plan.

NCRR's four intramural research programs and branches provide critical research technologies, resources, and services to NIH scientists, administrators, and other staff. These include:

- biomedical engineering and instrumentation collaboration and service through the Biomedical Engineering and Instrumentation Program (see article above);
- professional and technical support consultation on animal care and research through the Veterinary Resources Program;
- literature, referral, translation, and information resources through the NIH Library operated by the Library Branch; and
- visual documentation of scientific data, research programs, and events through the Medical Arts and Photography Branch.

Vaitukaitis asks that you respond by July 15 to three questions on the FAX-BACK sheet on page 20. ■

Fogarty Celebrates 25 Years of Enriching NIH Science and Culture

by Seema Kumar

In 1968, the newly established Fogarty International Center (FIC) invited its first scholar-in-residence, Uriel Littauer of the Weizmann Institute in Rehovot, Israel, to work with Marshall Nirenberg of NHLBI. To this day, Littauer and Nirenberg interact, and this year, their collaboration and the center that catalyzed it both turn 25 years old.

During these 25 years, 195 leading scientists from 28 nations and the United States have pitched their scientific tents at NIH to work with intramural colleagues on research of mutual interest. Among the visitors were four Nobel laureates: Daniel Bovet and Rita Levi-Montalcini of Italy, Ragnar Granit of Sweden, and Sir Hans Krebs of England. These interactions, says Jack Schmidt, chief of the Scholars-in-Residence Program, have resulted in increased international dialogue and collaborations, publication of hundreds of scientific papers and books, and scores of international conferences involving many of the world's leading biomedical scientists.

FIC continues to enhance the scientific and intellectual milieu at NIH and catalyze important studies in biomedicine and international health. As the sample sketches below show, scholars come from a variety of scientific and cultural backgrounds. However, each is recognized by his or her peers as an outstanding contributor to a discipline relevant to NIH's mission, has international stature, and has potential for effective interaction with NIH staff and other scholars in the program. For more information on the scholars or the program, call Schmidt at 496-4161.

Zilton Andrade *to 8/31/93*
Andrade has published many key papers about his research on the anatomy, pathology and immunopathology of schistosomiasis, Chagas' disease and leishmaniasis. His seminal studies of Chagas' myocarditis and hepatic complications of schistosomiasis are particularly notable. Andrade directs the Goncalo Moniz Research Center, Oswaldo Cruz Foundation, Salvador, Bahia, Brazil. NIAID's Allen Cheever nominated Andrade.

Adolph Graessmann *to 9/30/93*
Graessmann is best known for developing the microinjection technique now used worldwide to transfer known amounts of DNA, RNA, or protein components into mammalian cells. His work showed the technical feasibility of gene transfer and paved the way for recent research advances in viral-genome expression and cellular transformation by DNA tumor viruses. Graessmann is a professor and is executive director of the Institute of Molecular Biology and Biochemistry, Free University, Berlin. Heiner Westphal of NICHD nominated Graessmann.

Peter Gruss *to 8/1/93*
Gruss gained international recognition for his studies on homeobox genes and the molecular biology of mammalian development, particularly in the burgeoning field of the molecular embryology of mice. His research on the mechanisms that control pattern formation in embryogenesis, organogenesis, and cell differentiation has been seminal in this field. Gruss heads the Department of Molecular Cell Biology at the Max Planck Institute for Biophysical Chemistry, Göttingen, Germany. Gruss was nominated by Heiner Westphal of NICHD.

Tasuku Honjo *to 9/5/93*
Professor of medical chemistry at Kyoto University, Honjo is a top scientist in molecular immunology. He has done pioneering work on the molecular genetics of immunoglobulin heavy chains and on the mechanism of antibody-class switching. Honjo's work has contributed greatly to the understanding of lymphocyte development and function. Igor Dawid of NICHD nominated Honjo.

Abraham Loyter *to 8/31/93*
Trained as a biochemist, Loyter has made important contributions to the understanding of the fundamental mechanisms of membrane fusion and to its application to biotechnology and to clinical problems. His current interests include implanting membrane receptors and transport systems into target membranes; targeting drugs and toxins to tumor cells; elucidating mechanisms of viral infection and developing anti-viral agents; and transferring macromolecules and genetic material into cells. Loyter is chairman of the Institute of Life Sciences, The Hebrew University of Jerusalem. Loyter was nominated by Robert Blumenthal of NCI.

Manuel Morales *7/1/93 to 9/30/93*
Morales is an adjunct professor of physiology at the University of the Pacific in San Francisco, Calif., and an emeritus professor of biophysics at the University of California at San Francisco. He is known principally for his research on the biophysics and biochemistry of muscle contraction and has made major contributions to enzyme-kinetics theory. Through the use of novel fluorescence-spectroscopy techniques, he has contributed to current thought on energy transduction in muscle. Richard Podolsky of NIAMS nominated Morales.

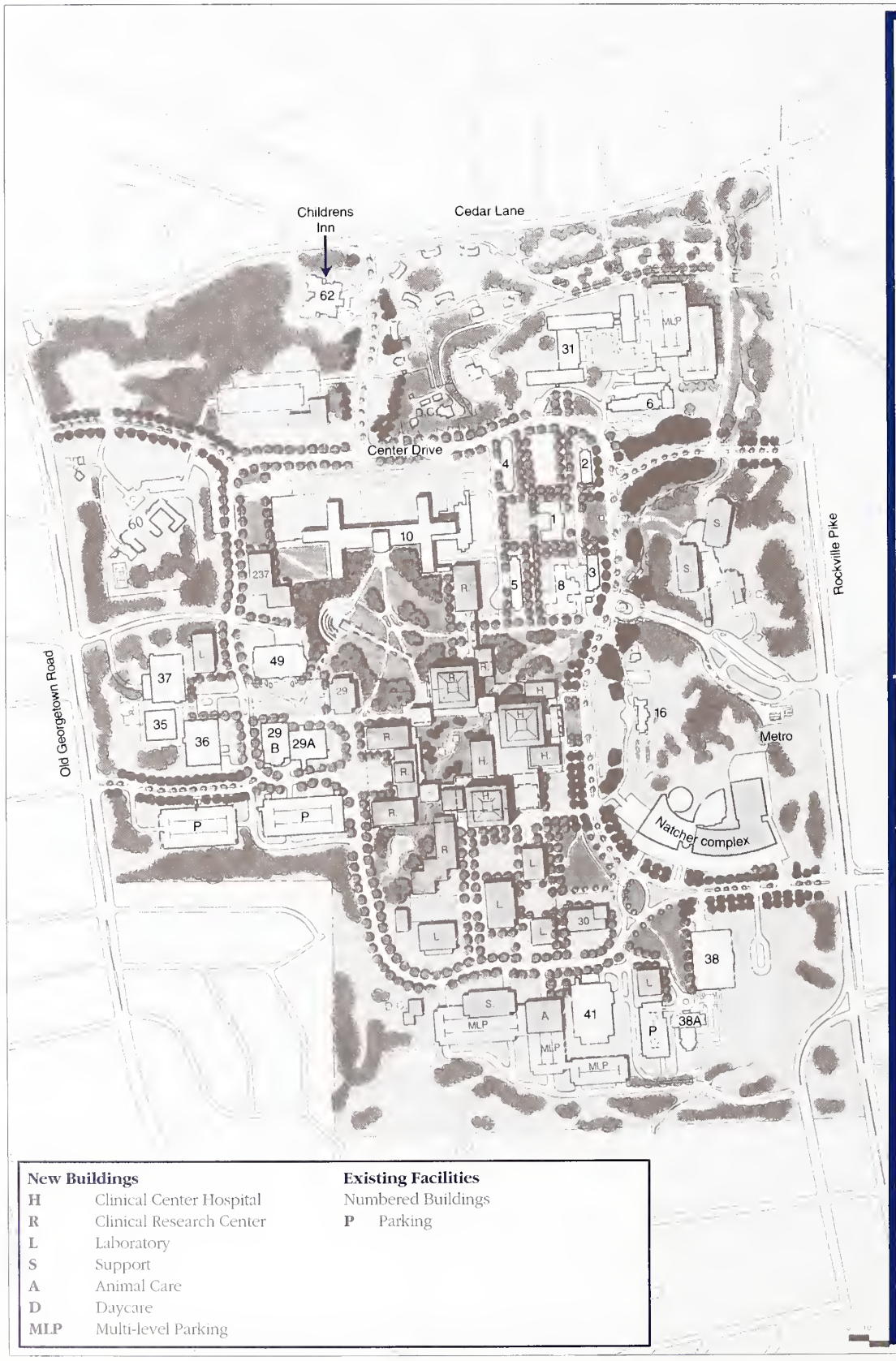
Richard Perham *to 7/31/93*
Chairman of the Department of Biochemistry at Cambridge University, Perham is an international authority on structure-function relationships in proteins, having been one of the first to apply nuclear magnetic resonance (NMR) spectroscopy and site-directed mutagenesis to such analyses. In recent years, he has concentrated on the function of multienzyme complexes, particularly the pyruvate dehydrogenase complex, and on studies of polypeptide-chain mobility. Darrell Liu of the Center for Biologics Evaluation and Research (CBER)/FDA, nominated Perham.

Wojciech Stec *to 7/2/93*
Stec is recognized as one of the world's experts in phosphorus chemistry, having made major contributions to the understanding of the basic stereochemistry and reactions of organophosphorus compounds. His work on the phosphorothioate chemistry of oligonucleotides and methods to synthesize stable oligodeoxynucleosides led to the current interest in the potential value of using anti-sense DNA to treat viral infections and some cancers. Stec is head of the Department of Bioorganic Chemistry, Center for Molecular and Macromolecular Studies, Polish Academy of Sciences, Lodz. Stec was nominated by Darrell Liu of CBER/FDA. ■

Alternative A

The Park

The NIH
Bethes



New Buildings

H	Clinical Center Hospital
R	Clinical Research Center
L	Laboratory
S	Support
A	Animal Care
D	Daycare
MLP	Multi-level Parking

Existing Facilities

Numbered Buildings

P Parking

"The Park" Which Would

Teams of planners have nar rowed the field of candi dates to two alternativ campus master plans for NIH Bethesda facilities, including replacement for the Clinical Cen ter Hospital (H) and associate research (R) buildings.

Early this year, the Facilitie Planning Office and consultants a Oudens + Knoop and Florance Eichbaum Esocoff King Architect prepared five "schemes" for the NIH campus of the future. In April, they presented these schemes to representatives of the PHS, regional planning commis sions, and NIH scientific and engi neering staff and the Facilities Planning Committee. On the basis of the feedback that they got, the planners chose the best features from the five schemes and incor porated them into the two pro posed master plans that appear here. In late May these master plans were presented to NIH employees and the public. The final master plan will be selected and drafted by December.

In devising a master plan, "the toughest problem is accommodat ing what we know will be the needs of NIH over the next 20 years on this site," says Stella Ser ras-Fiotes, NIH's senior master planner in the Facilities Planning Office. Serras-Fiotes says that although the campus site is large enough to house all of NIH, com munity and legal restrictions on traffic and its attendant air pollu tion will force "outplacing" — locating some parts of NIH off campus. "We're still working on the numbers," says Serras-Fiotes, "but for the year 2013, we are roughly estimating we will have 21,800 on campus and approxi-

STERPLAN CAMPUS

Alternative B

THE QUAD

"THE QUAD" CAMPUS CHOOSE?

nately 4,800 off campus, so there vill continue to be a need for off- ite facilities to house all of our ctivities."

The plan will be implemented radually over the next 20 years. A lot of what happens depends n funding," Serras-Fiotes says. he first parts of the plan sched- led for implementation will be eplacement labs for buildings 2, , and 7. This work will follow ompletion of the Natcher com- lex, now under construction.

Members of NIH's Facilities lanning Committee have veighed in with a preference for ne more formal, academic "quad" esign. This plan pulls supporting esearch buildings close to the linical Center and delineates the rganization of the campus more learly. Thomas Eichbaum, one f the lead architects for the mas- er plan, says the idea behind the park" design was to incorporate ome "very beautiful amenities of ne site—like the poplar forest at ne northwest corner, the stream t the northeast corner, the lawn t the southeast corner, and the ark at the southwest corner — nd bring those natural attributes nto the core" of the campus. The rchitects complement the land- cape-centered design with a less gid, more naturalistic arrange- ent of buildings "*in* an open pace rather than *forming* the pen space," Eichbaum says. But erras-Fiotes notes that the infor- ality of the "park" is more prone compromise of the plan and ould be more expensive to nplement. "Nevertheless," she ays, "we are confident that we ill be able to preserve some fea- ures of the naturalistic plan in the nal master plan." —*C.H.* ■

Recently Tenured

by Celia Hooper

A Folate-Transport Focus

Patrick Elwood's research focuses on proteins that bind and transport folate and antifolate into mammalian cells. In his recent studies, he cloned and characterized a family of genes encoding these receptor proteins, which are located in the cell membrane.

Folate is an essential vitamin involved in intermediate metabolism, including synthesis of DNA and RNA. But there is additional significance to Elwood's work. He observed that the level of expression of the folate-transport genes in mammalian cells correlates with their sensitivity to classic antifolate chemotherapeutic agents, such as methotrexate.

"We are asking specific questions about how the proteins work—the structure-function relationships. What does the binding site look like? How do these proteins attach to the membrane?" asks Elwood. Answers to these questions "might allow us to develop drugs that work better—that act more selectively in tumors," he says.

Among other projects, Elwood is working on a more sensitive, more specific in vivo test for detecting the folate-transport proteins. Such a test, reflecting the level of expression of the proteins, could predict tumor sensitivity or resistance to antifolate drugs. Manipulation of the proteins' expression or anchoring in the membrane in malignant tissue might be used to expand the therapeutic window for antitumor drugs.

Two idiosyncrasies of the folate-transport proteins are their unique DNA sequence and the mechanism whereby they internalize folate. Elwood says there are no genes with substantial homology to the folate-transport genes, and "the exact nature of internalization is not known, but it does not appear to be classic endocytosis via clathrin-coated pits." Instead, a unique endocytotic mechanism appears to be operating.

Elwood earned his M.D. from the University of Nebraska in 1975 and was trained in oncology and hematology at the University of Colorado, where he first characterized a folate-transport protein. He came to NIH in 1987 and now is head of the Section of Experimental Hematology at the NCI Clinical Oncology Program's Medicine Branch, Division of Cancer Treatment. ■

Scientists Recently Tenured

Anthony S. Basile, NIDDK
Dimiter Dimitrov, NCI
Neal Epstein, NHLBI
Lee J. Helman, NCI
Polly C.E. Matzinger, NIAID
Sanai Sato, M.D, NEI
Thomas J. Walsh, NCI

Courting a Curious Vascular Growth and Permeability Factor

Marsha Merrill studies a secreted protein called vascular permeability factor (VPF). And the more she learns, the more she has to learn. In 1986, Merrill and her colleagues extracted VPF from cultures of brain tumor cells. Other research groups had observed that some factor produced by other tumors also increased the permeability of blood vessels. This factor was named VPF when it was isolated in 1990. Merrill began studying VPF in hopes of gaining insight into one of the most critical problems associated with brain tumors. "The leakiness of the vasculature in tumors causes edema, pressure on the brain, pain—extensive morbidity and mortality," Merrill says. She found that VPF mRNA is expressed at low levels in normal glia and neurons, and in non-brain tissues, but that expression is highly elevated in some tumors.

Merrill shifted all her attention to VPF three years ago, when the protein acquired a second identity and name—vascular endothelial growth factor (VEGF). Other groups of scientists had been pursuing a substance, produced by bovine pituitary cells, that stimulates growth of blood vessels. "Early in 1990, it became clear, as the two groups of scientists purified and cloned these factors [VPF and VEGF], that it was the same protein," says Merrill.

The dual functions of VPF-VEGF only made the fact that the factor's mRNA is produced by normal brain cells more startling. "In addition to gliomas and other central nervous system tumors, we looked at normal brain tissues and found that VPF mRNA is expressed there as well," says Merrill. "That was really quite a surprise to us. The two activities that this factor is known for—induction of capillary permeability and stimulating the growth of endothelial cells—are not processes that are happening in the normal adult brain. We are not sure why it is there."

Merrill is now trying to find out. Tumors churn out large amounts of functional VPF-VEGF protein, but because the protein is undetectable in samples of normal brain tissues, Merrill is

Corrections

In our April issue, we obtained the wrong list of promotions and made several errors in the box headed "Recently Tenured." The names of **Jacqueline N. Crawley, Alan P. Wolffe, Hua Su** (whose name was misspelled), and **Michael Steller** should not have been listed. Crawley and Wolffe received promotions recently, but have been tenured for several years. Su recently became a permanent collaborative scientist, and Steller was hired with tenure.

unsure whether normal cells do not translate the VPF-VEGF mRNA or produce just traces of the protein that are instantly taken up by endothelial cells. Since survival of all tissues in the body requires intimate contact with capillaries, it is conceivable that cells maintain a small supply of VPF mRNA just in case they are somehow cut off from their supply line and must quickly stimulate capillaries to release more nutrients or grow in their direction. Angiogenesis, or vascularization, in tumors and after injury support this scenario.

Getting direct evidence on the function of VPF-VEGF will require better tools. Merrill is now developing more-sensitive antibodies for detecting various forms of VPF-VEGF. She wants to explore signals, such as hypoxia, that may turn on production of VPF-VEGF. Stimulating re-vascularization could be helpful in treating stroke. She also wants to explore factors that inhibit VPF. The only treatment used now for edema caused by brain tumors is high doses of steroids. "We are looking at steroid analogs that have fewer side effects to see if we can get the same reduction in vascular leakage," says Merrill. Her role in this work will be to try to understand how steroids interact with VPF. "This factor is relatively new to the scene...," says Merrill. "There is so much to do, you almost don't know where to start!"

Merrill earned her Ph.D. at the University of Wisconsin at Madison, and came to NIH in 1983, starting out as an NCI postdoctoral fellow. She is now a member of NINDS' Surgical Neurology Branch. ■

Extracting Exciting Unknowns

Natural products chemist **Kirk Gustafson** has the privilege—and frustration—of a research life of pure discovery. Gustafson's job is to isolate and purify new anticancer and antiHIV drug candidates from promising crude extracts taken from plants, marine organisms, and microbes.

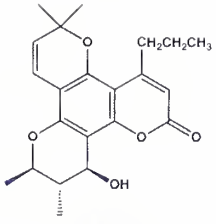
Gustafson's work begins after his colleagues at NCI-Frederick identify extracts that block HIV infection in cell cultures or that have specific inhibitory activity against some members of a panel of 60 tumor-cell lines. Gustafson's colleagues hand him a vial of tar-like paste—a gemisch of hundreds of chemicals. Gustafson then opens his bag of chemical tricks and goes to work pulling the pure active ingredient out of the jumbled mess.

"It's hard to predict what you are going to be working on next," Gustafson says of his job. "I would say I've done 12 to 15 of these isolations" since joining the NCI lab in 1987. The principle determining which glop he will work on next is the same principle that guides his extraction processes: He pursues the substances with the best anti-HIV or anti-tumor activity. "Each new extract is a unique entity that requires a different approach, especially if we are trying to optimize the isolation," says Gustafson, who is currently working on four isolation projects.

One of the most interesting series of compounds that Gustafson helped isolate was derived from a species of Calophyllum, a Malaysian tree in the plant family Guttiferae. These anti-HIV compounds, called calanolides, are completely novel molecules—prenylated coumarin compounds—that inhibit HIV reverse transcriptase. The calanolides have been selected by the NCI Decision Network Committee for NCI preclinical development, and one or more of this class of compounds may eventually go into clinical trails. Gustafson says that one exciting aspect of the calanolides is that they appear to be active against strains of HIV that are resistant to 3'-azido-3',deoxythymidine (AZT) and non-nucleoside reverse transcriptase inhibitors.

Gustafson's Ph.D. and postdoctoral work focused on the natural-products chemistry of marine organisms, but since coming to NCI, he has worked primarily on extracts from land plants and blue-green algae.

Gustafson, who earned his Ph.D. at the University of British Columbia in Vancouver in 1984, did a postdoc at Scripps Institute of Oceanography in San Diego before coming to NCI. Gustafson is a staff scientist with the NCI Laboratory of Drug Discovery, Research, and Development at the Frederick Cancer Research and Development Center at Ft. Detrick. ■



Calanolide A

NIH "House-brand" HIV p24 Antibodies Available

Bruce Chesebro and his NIAID associate Kathy Wehrly at the Rocky Mountain Laboratories' Laboratory of Persistent Viral Diseases have developed their own sensitive "house brand" of monoclonal antibody that detects p24 Gag, a core protein of the human immunodeficiency virus-type 1 (HIV-1).

Commercially prepared, microtitre coated assay trays for detecting HIV p24 in 100 samples can cost upwards of $300. "A lot of people complain about the cost" of commercial preparations, Chesebro says. The trays, coated with p24 antibodies, are used for the ELISA antigen-capture assay. Chesebro's version of the antibody works well for immunofluorescence assays for detecting HIV in fixed tissue as well as blood and other fluid samples taken for clinical or basic studies. "We found that this antibody that we have works well to coat microtitre trays, and it makes it a lot cheaper to do the assays," says Chesebro. "I wanted to share this with fellow researchers."

Chesebro and Wehrly describe how to purify the antibodies from hybridoma 183 (clone H12-5C) in an article in the March 1993 issue of *The Courier*, the newsletter of the NIH AIDS Research and Reference Reagent Program. The hybridoma cells were developed by Chesebro and Syntex, a commercial partner that elected not to patent the reagent. "I've sent this to a lot of labs, and they like it a lot," says Chesebro. To order hybridoma cells from the AIDS repository, contact Martha Matocha, NIH AIDS Research and Reference Reagent Program, 685 Lofstrand Lane, Rockville Md. 20850 Phone: (301) 340-0245; Fax: (301) 340-9245. ■

Immune Response to HIV: Analysis of a Possible Success

By Mario Clerici, Experimental Immunology Branch, NCI

One of the most exciting recent findings in AIDS research is that harmless — and possibly protective — human encounters with human immunodeficiency virus (HIV) may occur in nature. The significance of this observation is that the interaction between HIV and the immune system does not invariably result in the infection of the exposed individual. Analysis of the immunologically successful response to HIV has revealed that protection against HIV infection or delayed progression to AIDS may be associated with cell-mediated, but not with humoral, immunity. In this commentary, I summarize the observations that have led to this hypothesis and analyze the dichotomy between cellular and humoral immunity in the context of the recent functional subdivision of human T-helper lymphocytes in two distinct populations: T-helper 1 (TH1) and T-helper 2 (TH2).

HIV-Exposed Individuals: Possible Protective Role of Cellular Immunity

A series of reports suggests that HIV-specific cell-mediated immunity may be protective against infection or against the progression of disease (*for review, see ref. 1*). First, exposure to HIV in the absence of seroconversion is associated with the exclusive presence of HIV-specific T lymphocytes, functionally characterized as cells producing interleukin 2 (IL-2). HIV-specific, IL-2 - producing lymphocytes have been detected in many individuals who do not seroconvert to produce HIV-specific antibodies, despite their belonging to groups at risk for HIV infection. These at-risk groups include gay men, intravenous-drug users, sexual partners of HIV-seropositive (HIV+) individuals, health-care workers exposed to HIV through needle sticks, and newborn infants of HIV+ mothers. Moreover, we have recently observed that HIV infection in neonates of HIV+ mothers is associated with the absence of HIV-specific T-lymphocyte responses.

	Predicted (TH2-like)	Observed
B cell activation and hypergammaglobulinemia	✔	✔
Hyper IgE and allergies	✔	✔
Reduced DTH[1]	✔	✔
Reduced CTL activity[2]	✔	✔
Reduced in vitro T cell proliferation	✔	✔
Reduced production of IL-2	✔	✔
Reduced production of IFN-γ	✔	✔
Increased production of IL-4	✔	✔
Increased production of IL-6	✔	✔
Increased production of IL-10	✔	✔

1 DTH= Delayed type hypersensitivity
2 CTL= Cytotoxic T lymphocytes

Table 1. *Concordance between the predicted symptomatology of a TH2-like condition and the symptomatology observed in HIV infection.*

A second line of evidence comes from mucosal exposure of primates. Intrarectal exposure of macaques to graded doses of simian immunodeficiency virus (SIV) induces a biphasic response in which macaques exposed to the highest viral doses become seropositive, show a decline in the number of CD4+ T lymphocytes, develop simian AIDS, and eventually die, whereas macaques exposed to lower doses of SIV neither seroconvert nor develop any symptoms. Although the immunologic profile of the macaques exposed to high doses of SIV is characterized by high titers of SIV-specific antibodies and weak or absent SIV-specific T-lymphocytes, the macaques exposed to lower viral doses exhibit an SIV-specific T-lymphocyte response associated with an absence of anti-SIV antibodies.

A third line of evidence is provided by experiments in which the genetically deficient immune system of severe combined immunodeficient (SCID) mice was reconstituted with human peripheral blood leukocytes (PBLs) from volunteers who had been immunized with HIV candidate vaccines and then challenged with HIV. In these experiments, HIV infection occurred in mice reconstituted with PBL from volunteers in whom the vaccine had induced HIV-specific antibodies, but not in mice reconstituted with PBLs from volunteers in whom the vaccine induced HIV-specific T lymphocytes.

Fourth, macaques immunized with live, genetically manipulated, defective SIV were protected when challenged with lethal doses of SIV. The protection was not correlated with the titers of SIV-specific neutralizing antibodies. Fifth, the early dramatic decline of virus titer subsequent to primary HIV and SIV infection follows the generation of virus-specific T-lymphocytes, but precedes the generation of specific antibodies. Sixth, the progression to disease in HIV-infected individuals is associated with a continuous decline in T-lymphocyte function, but is not associated with changes in the production of antibodies. Taken together, these lines of evidence suggest that cellular immunity is more important than humoral immunity for successfully impeding infection by HIV and SIV, and is responsible for the long asymptomatic period that follows HIV and SIV infection. The mechanisms by which cellular immunity exerts this protective action are probably complex: IL-2 and γ interferon (γ-IFN) can have direct antiviral effects and can also induce the generation of cytotoxic T lymphocytes (CTLs), an effective defense in controlling the replication of intracellular organisms (*for review, see ref. 2*).

This dichotomy between antibody-mediated and cell-mediated immune protection is not exclusive to HIV infection. Activation of B lymphocytes and production of antibodies has been shown to be useful in the defense against cell-free agents and toxins such as pneumococcus and tetanus toxins. In contrast, triggering of cell-mediated immunity appears to be effective against infections by pathogens and parasites that reside within the cells of their hosts, such as *Leishmania, Mycobacterium, Toxoplasma,* and *Treponema* species.

Functional Dichotomy of the Immune Response: the TH1-TH2 Hypothesis

The mechanisms that regulate induction of distinct immune responses to different pathogens have recently been clarified by the identification in mice and humans of two functionally distinct types of T-helper lymphocytes, TH1 and TH2. TH1

continued on page 16.

GENETICS OF HUMAN RENAL CELL CARCINOMA

By Berton Zbar, Michael I. Lerman, and W. Marston Linehan
(BZ, MIL, Laboratory of Immunobiology; WML, Urologic Oncology Section, Surgery Branch, NCI)

Until recently, little was known about the genetic basis of human renal cell carcinoma. A turning point came in 1979, when Cohen et al. described a remarkable family with members affected with bilateral, multifocal renal cell carcinoma (1). Affected family members inherited a balanced translocation between the short arm of chromosome 3 (3p) and the long arm of chromosome 8; nonaffected family members did not inherit the balanced translocation. These observations suggested the presence of a specific gene located on chromosome 3 or 8 that played a critical role in the origin of renal cell carcinoma. Cytogenetic analysis of sporadic renal cell carcinomas, in which deletion of chromosome 3p was consistently found, supplemented the observations of Cohen et al. (1). The introduction of molecular methods for detecting rearrangements of the genome facilitated detailed characterization of tumors.

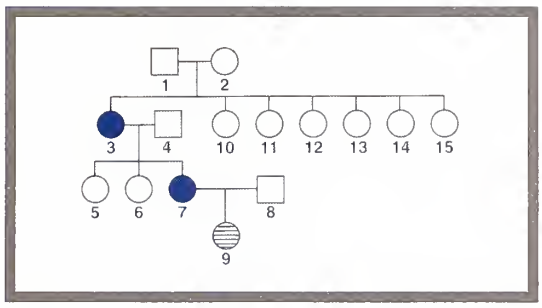


FIGURE 1. *Detection of rearrangement mutations in constitutional DNA of patients with VHL disease. The pedigree shows affected individuals (filled circles) and an individual predicted to be affected (hatched circle). In this family, the novel DNA fragment appeared coincident with the disease in individual #3, and the novel DNA fragment and disease were transmitted to the next generation.*

In 1987, our laboratory reported that sporadic renal cell carcinomas were characterized by a loss of alleles on the short arm of chromosome 3 (2). Subsequent observations have confirmed that 3p deletions are consistently associated with renal cell carcinoma. Carcinoma of the kidney is diagnosed in about 27,000 individuals in the United States each year; about 10,000 deaths from kidney cancer occur each year.

We speculated that a gene required for the maintenance of normal growth of proximal renal tubular cells was located on chromosome 3p. We called this gene the "renal cell carcinoma gene." We were influenced by the work of Alfred Knudson who postulated that cancers arise as a consequence of inactivation of both copies of critical genes, and that sporadic and hereditary tumors are a manifestation of mutation of the same gene (3).

This simple, elegant theory suggested that analysis of the inherited forms of a neoplasm should make it possible to identify the gene responsible for both the inherited and sporadic form of the neoplasm. Thus, we set out to try to identify the postulated renal cell carcinoma gene. We decided to study an inherited illness called von Hippel-Lindau disease (VHL) because it was the most common inherited form of renal cell carcinoma.

VHL is a multisystem neoplastic disorder. Individuals who inherit the disease gene have a predisposition to develop not only renal cell carcinoma but vascular tumors of the retina and central nervous system, and pheochromocytomas (vascular tumors of chromaffin tissue of the adrenal medulla or sympathetic paraganglia). Virtually all individuals who inherit the disease gene will have some manifestations of the disease during their lifetimes, but its severity varies. Some individuals have lesions limited to the eyes and have visual impairment; others have involvement of multiple organ systems and require surgical treatment of tumors of the kidneys, spinal cord, and brain.

We used positional cloning strategies to isolate the VHL gene. After identifying families with the illness, we used linkage analysis to find markers that flanked the disease gene and also to find a marker that did not recombine with the disease gene. The marker that did not recombine with the disease gene was, in turn, used to prepare a long-range restriction map of the VHL region. This map led us to germline rearrangements in three unrelated individuals with VHL that proved to be nested deletions ranging in size from 100 to 380 kb. After isolating yeast artificial chromosomes from the VHL region, we isolated a series of overlapping cosmids, and one of these (cos11) was found to be deleted in all three patients with the germ-line deletions. Two cDNAs were isolated with cos11 and one, gp7, was found to be a good candidate for the VHL gene.

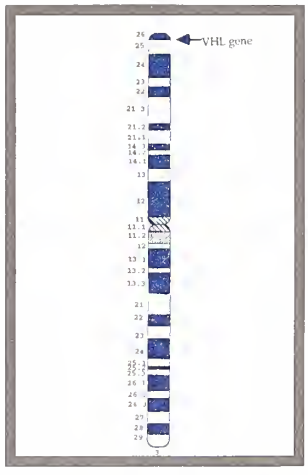


FIGURE 2. *Ideogram of chromosome 3. The VHL gene is located near the tip of the short arm of chromosome 3 at the junction of bands 3p25 and 3p26.*

The gp7 cDNA detected rearrangments in germ-line DNA of 12% of unrelated VHL patients. These rearrangements were inherited with the disease, and in patients with new VHL mutations, the rearrangements appeared coincident with the disease. The gp7 cDNA also detected single-strand conformational polymorphisms (SSCPs) in the germ-line DNA of VHL patients, and in three patients, the nucleotide changes responsible for these conformational polymorphisms were identified (4).

The gp 7 cDNA detects a 6- and a 6.5-kb mRNA and is expressed in all tissues that have been tested, including heart, skeletal muscle, brain, placenta, lung, liver, kidney, pancreas, and prostate. The sequence of the gp 7 cDNA shows no homology to other known genes with the exception of an acidic repeat domain that is similar to the procyclic surface membrane protein of *Trypanosoma brucei*. The presence of the acidic repeat domain in the putative VHL protein suggests that it may be localized on the cell membrane and may be involved in signal transduction or in establishing cell-to-cell or cell-to-matrix contact.

Of particular interest is that the gp 7 cDNA detects mutations in sporadic renal cell carcinomas. These mutations have been

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IMMUNE RESPONSE TO HIV

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lymphocytes secrete γ-IFN and IL-2 and promote mainly cellular immunity; TH2 lymphocytes secrete IL-4, IL-5, IL-6, and IL-10, and stimulate the activation of B lymphocytes and the generation of antibodies. The activation of a TH1-type response induces suppression of a TH2-like response, and vice versa. This tendency toward reciprocity is mediated through the secretion of cross-regulating cytokines as γ-IFN suppresses TH2 lymphocytes and IL-4 and IL-10 suppress TH1 lymphocytes (for review, see ref. 3).

We now suspect that immune resistance to HIV may be related to a TH1-dominated response. Conversely, the symptomatology of HIV infection, characterized by stimulation of B lymphocytes with hypergammaglobulinemia and precocious and profound suppression of the function of T lymphocytes, appears to us to resemble a TH2-dominated response. For this reason, we recently tested the hypothesis that HIV infection is associated with a TH1-to-TH2 switch.

To test this hypothesis, we measured the expression of TH1 cytokines (IL-2 and γ-IFN) and TH2 cytokines (IL-4 and IL-10) in a few dozen HIV-seronegative (HIV-) individuals exposed to HIV, as well as in hundreds of HIV+ individuals, most of whom were asymptomatic. The results showed, first, the presence of high concentrations of IL-2 but low concentrations of IL-4 and IL-10 in people at risk of exposure to HIV (M. Clerici and G. Shearer, unpublished observations). Second, two of six high-risk HIV-, T-cell-positive gay men enrolled in a longitudinal study eventually seroconverted; in both cases, appearance of antibody and a positive polymerase chain reaction (PCR) were associated with a sharp decline in cell-mediated immunity, as shown by a dramatic loss in the in vitro HIV-stimulated production of IL-2. Third, the majority (>65%) of HIV+ asymptomatic individuals showed a time-dependent loss in the ability to produce IL-2 and γ-IFN when stimulated, concomitant with a dramatic increase in the production of IL-4 and IL-10 (4).

This switch from a TH1-like to a TH2-like pattern in HIV infection has been analyzed and confirmed at several levels: with cytokine-specific mRNA by PCR analysis; with cytokine concentrations by ELISA; and with isolation of PBL clones in HIV+ patients followed over time. The concordance between the predicted symptomatology of a TH-2-like condition and that observed in HIV infection is summarized in Table 1. Additionally, the switch from a TH1-like to a TH2-like condition in HIV+ individuals has been found to be predictive of patients' prognosis. Over a 3 to 5-year-period, a TH2-like condition in HIV+ asymptomatic patients was statistically associated with 1) a decline in the number of CD4+ T lymphocytes, 2) progression to AIDS, and 3) progression to death (5; M. J. Dolan, M. Clerici, G.M. Shearer, unpublished observations). Based on these observations, we recently suggested that a TH1-like pattern of cytokine production is associated with resistance to HIV infection, whereas a TH2-like pattern is characteristic of the progressive phase of disease (6). These findings may have therapeutic implications, because protocols can be developed based on TH1 cytokines or on antibodies against TH2 cytokines, with the double objective of preventing a TH1-to-TH2 switch and restoring a TH1-like immune-profile condition in HIV+ patients showing a low IL-2 and γ-IFN and a high IL-4 and IL-10 profile. Finally, because a TH1-type response may be more effective in protecting against HIV infection, it was suggested recently that designing candidate AIDS vaccines to elicit strong anti-HIV humoral immunity may not be the most effective strategy (7). We believe that vaccines that augment HIV-specific, TH1-type cell-mediated immune responses will prove more effective.

Acknowledgment

I am grateful to my friend and boss, Gene M. Shearer, for his precious and continuous support. ■

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RENAL CELL CARCINOMA

continued from page 15.

detected by Southern blot analysis but are most readily detectable by single-strand conformational polymorphisms. By DNA sequence determination, we have found that these tumors have small deletions within exons of the VHL gene. This observation suggests that the VHL gene plays a major role in the origin of sporadic renal cell carcinomas and is, in fact, the long-sought renal cell carcinoma gene.

Evidence suggests that there is more than one renal cell carcinoma gene and that there is a correspondence between the histology of the renal tumor and the causative renal cell carcinoma gene. Mutation of the VHL gene produces renal tumors composed of clear cells with a solid growth pattern. Tumors with a papillary growth pattern are probably produced by mutation of another gene, which is not located on chromosome 3.

Like several other genes responsible for hereditary neoplastic disorders, the VHL gene is exquisitely tissue specific. For example, one inherited disorder confers a predisposition to develop tumors of the auditory nerve, whereas another confers a predisposition to develop tumors of the peripheral nerves. Despite the restricted tumor spectrum, the genes are widely expressed. The puzzle is why inheritance of an inactivated copy of a widely expressed gene should produce tumors in just a few organ systems.

The availability of a cDNA for the VHL gene opens up a large number of avenues for investigation. Our future plans include identifying the protein product of the gene and localizing and defining its cellular function; studying the role of this gene in the embryological development of the kidney and brain; and characterizing the mutation spectrum in sporadic renal cell carcinoma and other human tumors. From the biological point of view, a particularly challenging problem is the puzzle of tissue specificity. ■

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NIH INTRAMURAL WOMEN SCIENTISTS
continued from page 1.

- Women and men scientists are not well informed about NIH tenure and promotion policies. This situation is the result of poor communication between women and men scientists and their Lab Chiefs and Scientific Directors.
- NIH does not have uniform tenure and promotion policies.

Recommendations
On the basis of its findings, the task force offers the following recommendations:
- A Woman Scientist Advisor to the Scientific Director of each institute, center, or division (ICD) should be appointed to increase and enhance effective communication between women scientists and the administration.
- Compensation, should be equalized throughout NIH, where appropriate.
- A uniform tenure plan should be established at NIH.
- A uniform NIH promotion plan should be established, implemented, monitored, and evaluated.
- The visibility of intramural women scientists of all racial and ethnic groups should be increased by including them in greater numbers at NIH forums and at NIH-supported meetings.
- A family-leave flextime plan for NIH should be established, uniformly implemented, monitored, and evaluated.
- The position of NIH Woman Scientist Coordinator should be established in the Office of the Deputy Director for Intramural Research, to implement the recommendations of this task force and to communicate the concerns of intramural women scientists, including those of minority women scientists, to NIH's Deputy Director for Intramural Research and its Director.

APPOINT WOMEN SCIENTIST ADVISORS TO SCIENTIFIC DIRECTORS

Issue
Intramural women scientists would like the NIH scientific community to become more aware of problems and issues specific to women scientists at NIH. Poor communication between intramural women scientists and Scientific Directors appears to be responsible for the lack of attention to these issues. Frequently, women scientists also feel isolated. They do not know other women scientists who might serve as mentors or with whom they might consult when problems arise.

Recommendation
Each ICD should select an intramural Woman Scientist Advisor to her institute's, center's, or division's representative to the Board of Scientific Directors. The Advisor should be a senior woman scientist of high standing who is familiar with NIH. All efforts of the Woman Scientist Advisor should be coordinated with the NIH Federal Women's Program Manager, Office of Equal Opportunity. The specific duties and activities of the Advisor would include
- serving as a liaison for the women in their institute, center, or division to the NIH Federal Women's Program Manager, Office of Equal Opportunity;
- advising the Scientific Director on establishing, implementating, monitoring, and evaluating strategies for enhancing and promoting career development of all women scientists, including those of diverse racial and ethnic background;
- informing the Scientific Director about priority issues of concern to women scientists, such as recruitment, retention, promotion, tenure, and enhancement of scientific visibility;
- serving as a source of information for women scientists in her ICD and as a conduit to the Scientific Director for discussion of problems perceived to affect women scientists. Individual discrimination and harassment problems will still be directed to the Equal Employment Opportunity Officer at the appropriate ICD or to the NIH Office of Equal Opportunity;
- attending the Lab Chiefs' meetings as a representative of women scientists
- creating a networking system to promote communication among women scientists and preparing and distributing a list of senior scientists at each ICD who are willing to act as mentors;
- providing names of women scientists to serve on Institute or NIH committees dealing with scientific programs, promotion, or policy formulation, for the purpose of ensuring that these committees are responsive to women scientists' issues;
- meeting at least once a year with the Federal Women's Program Manager and the women of each ICD to discuss issues within the institute and NIH; and
- meeting at least twice a year with all the NIH Women Scientist Advisors, the Coordinator from the Office of the Deputy Director for Intramural Research, and the Federal Women's Program Manager, Office of Equal Opportunity, to communicate the women scientists' concerns and to network on NIH intramural programs.

Selection Process
Several Institutes have already selected Women Scientist Advisors. The process used to select the Advisor is up to the individual institute. One suggestion is for the Scientific Director, in conjunction with the institute's, center's, or division's member(s) or the Task Force on the Status of NIH Intramural Women, to organize a meeting of all the women scientists in the institute. Two candidates for the advisory position could be nominated during the meeting; the Scientific Director could then choose between them. The Advisor must hold an election within her Institute to either confirm her position or to select an Advisor acceptable to both the women of the Institute and the Scientific Director. All Advisors would serve for terms of two years. Once the Advisor had been selected, Institute members would be informed through a memo and a short presentation at the lab chiefs meetings. The Advisors from all the ICDs would make up an NIH committee that monitors issues of concern to intramural women scientists. As part of its function, the committee would bring concerns to the attention of the NIH Director, the Deputy Director for Intramural Research, and other appropriate officials, such as the Director of the Office of Research on Women's Health and the Director, Office of Equal Opportunity.

EQUAL PAY
Preliminary pay analysis

Issue
Many scientists had expressed concerns over pay differences between men and women scientists. So the Office of Education undertook studies to determine whether there existed any.

Any analysis of gender differences in compensation is complicated by a multiplicity of factors that affect levels of remuneration. These may include educational degrees, experience, productivity, peer recognition, and pay structure within an

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ICD. Some of these indicators may in turn be affected by other factors. For example, productivity may reflect not only creativity, discipline, and hard work, but also the monetary and human resources available to an investigator. A rigorous analysis that takes into account all the above elements is beyond the scope of this effort. The purpose of this analysis is to determine, albeit superficially, whether a pay differential exists between male and female scientists. The analysis is not designed to find the reasons for any apparent differentials, nor is the model sophisticated enough to provide a formula for corrective measures, should any be warranted.

The Office of Education selected pairs of men and women scientists from the intramural program of approximately 1200 tenured scientists, matching them for ICD, pay-plan, degree, and years-since-highest-degree. In cases where more than one match could be constructed (e.g., a female scientist could conceivably be matched with any one of perhaps 3 male scientists sharing her ICD, pay plan, degree, and years-since-highest-degree), all information was included by using the mean salary of all possible matches of males or females. In this way, 77 pairs were constructed representing 82 females and 102 males. *(See table below.)*

Number of Pairs	77	14	63
Degrees (M.D.s or Ph.D.s)	All pairs	M.D. pairs alone	Ph.D. pairs alone
Mean Salary (Men)	$74,886	$98,428	$69,654
Mean Salary (Women)	$71,605	$100,177	$65,255
Salary Difference (Men-Women)	$ 3,281	-$ 1,749	$ 4,399

For the 77 pairs, the salaries of men exceeded those of women by approximately $3,300. This difference in salaries differs significantly from zero (Wilcoxon signed rank test $p < 0.02$). In further breakdowns, perhaps due to the small sample size, the salary differential between male and female M.D.s did not differ significantly from zero; however, the salary differential between male and female Ph.D.s was significantly different from zero.

No matches were detected for the less than hundred tenured scientists holding both an M.D. and a Ph.D. degree. However, we detected errors in the recording of joint degrees in the pay database. When this error occurs, most commonly individuals are being listed as holding an M.D. alone when in fact they hold both an M.D. and a Ph.D. For this reason, the intramural community has been queried to confirm this data; however, less than one-third have responded to date. Although individuals holding joint degrees may represent a minority of the population, such errors would produce faulty matches and could skew the salary differentials. At present we are unable to estimate the magnitude of this possible error.

In summary, this analysis suggests that a gender-based differential in compensation may exist and offers reason for ICDs to proceed with more detailed individual reviews of salary.

Recommendations

- Each ICD must analyze the salary status of their men and women scientists and make adjustments to correct disparities and inequities, taking into account length of time from degree, productivity and type of research.
- Salary ranges for each level should be made available to all employees.

INCREASE THE VISIBILITY OF NIH INTRAMURAL WOMEN SCIENTISTS

Issue

Many NIH-sponsored scientific meetings, lectures, workshops, and programs (intramural and extramural) have a disturbingly low number of women speakers, as shown by examples to the right.

Currently, 34% of all Ph.D.s in the life sciences are women, making it unlikely that there are few qualified and talented women to include in these activities. Pool sizes for women Ph.D.s will be estimated for the periods in question to provide a denominator for these numbers; however, estimates of women Ph.D.s employed in the late 1980s in the life sciences (23.4% of Ph.D.s employed in the biological sciences and 29.1% of Ph.D.s employed in the medical sciences are women) suggest that women are underrepresented in these activites. Likewise, journal editorial boards and panels that solicit and make award nominations are disproportionately under-represented by women. This lack of participation diminishes women scientists' visibility and may delay or prevent their promotion to tenure. Lack of visibility further reduces the number of female role models, thereby wasting valuable scientific resources.

Recommendations

- NIH should encourage women scientists' full participation in all NIH-sponsored meetings, workshops, lectures, programs, and activities. NIH should encourage managers to nominate women for awards. Special efforts should be made to increase and enhance the visibility of minority women scientists.
- The NIH Director should distribute an annual, campus-wide memorandum emphasizing inclusion of women on program committees, awards panels, symposia, and journal editorial boards. The memorandum should be sent to all people reserving Masur, Lipsett, Lister Hill, and Wilson Hall, and to all Continuing Medical Education Program organizers.
- Scientific Directors should monitor these activities in their respective ICDs and submit an annual report to the NIH Director on (1) the participation of women scientists in intramural and extramural programs and (2) an accounting of the number of women nominated for awards. These reports should be moni-

Lecture	Total	Women
Dyer 1951 to 1990	36	1
Lecture Series 1953 to 1990	108	9
Jules Freund 1961 to 1974	13	0
Kinyoun 1979 to 1990	12	1
DeWitt Stetton 1982 to 1990	9	3
Marjorie Guthrie 1983 to 1987	5	0
Seymour Kreshover 1983 to 1990	8	2
Totals	**191**	**16**

Data Source: The NIH Almanac

tored by the Office of the Director, Office of Equal Opportunity and appropriate women's advisory panels.

■ The Division of Research Grants should expand the on-line consultant file to include more women and their areas of interest and expertise. The intramural community should be apprised of the availability of this resource and encouraged to use it to locate women scientists with sought-after expertise. The appropriate women's advisory panels and Women Scientists Advisors should be charged with this task and given necessary resources to perform it.

■ Criteria for NIH-supported scientific meetings (R13 grants) should be revised to include a requirement that conference managers submit an explanation, in writing, when women are not invited as speakers.

■ The NIH Director, ICD Directors, and Scientific Directors should provide leadership in concert with other agencies, such as National Science Foundation (NSF), Department of Energy (DOE), and Office of Naval Research (ONR) to devise an equitable policy for federally funded support of scientific conferences. Such a policy should be communicated to major professional organizations, encouraging them to adopt appropriate guidelines with regard to inclusion of women in privately funded meetings and on journal editorial boards and award panels.

■ Two yearly lectures should be established to present women speakers:

• The NIH nominee for the Women in Science and Engineering award (WISE) award and

• NIH women scientists sponsored by a to-be-established NIH women-scientists lecture series.

NIH WOMAN SCIENTISTS COORDINATOR

Issue

Task force recommendations need to be implemented, and issues of concern to women intramural scientists need to be communicated to the appropriate NIH leadership.

Recommendation

An NIH Women Scientists Coordinator position should be established within the Office of the Deputy Director for Intramural Research to implement task force recommendations and to communicate concerns affecting NIH intramural women and minority women scientists to NIH leadership. All efforts where appropriate should be coordinated with the Federal Women's Program Manager, Office of Equal Opportunity. The position should be established for at least five years with a yearly budget sufficient to accomplish the goals listed below. The Woman Scientist Coordinator would be responsible for

• implementing the recommendations from the Task Force on the Status of NIH Intramural Women Scientists;

• representing the Deputy Director for Intramural Research on matters concerning intramural women scientists;

• developing, with the Deputy Director for Intramural Research, Women Scientist Advisors, and other interested people, a memorandum defining the standard tenure process for NIH;

• determining the reason for departure from NIH by interviewing women and men scientists as they leave;

• reviewing the NIH Office of Education's annual report on tenure, pay, and promotion with the Deputy Director for Intramural Research;

• rewriting the Staff Fellow brochure to make it — especially the descriptions of the position requirements and expectations — easier to understand;

• meeting twice yearly with ICD Woman Scientist Advisors to review problems and accomplishments and set goals;

• serving as an NIH community resource on issues concerning NIH intramural women scientists;

• advising Deputy Director Intramural Research regarding possible actions against those not complying with NIH standards;

• distributing yearly to all NIH employees the NIH policy on *flexible* family leave;

• arranging at least two (spring and fall) NIH forums on subjects of interest to NIH women regarding tenure, pay, promotion, visibility, leadership, mentoring, etc, and transcribing tapes of these forums and preparing summaries for the Deputy Director, Intramural Research;

• maintaining a list of NIH women scientists and their fields of interest and indicating their availability to serve as speakers and mentors;

• publishing an annual directory of NIH women scientists by ICD;

• monitoring the number of women, including minority women, on NIH internal committees, on scientific advisory panels, at campus research meetings, etc., and sending a yearly memo to be signed by the NIH Director regarding inclusion of women and minority women on such committees, panels, etc;

• attending Scientific Directors and Deputy Director Intramural Research staff meetings;

• coordinating the NIH Women Scientists and WISE Lectures, i.e., soliciting names, making arrangements, etc;

• developing additional goals related to NIH women and minority women scientists;

• making efforts to recruit minority women, based on the small numbers of tenured minority women scientists.

Acknowledgments

The Task Force would like to thank the Deputy NIH Legal Advisor, Patricia A. Kovchak, for careful evaluation of this report. All data were prepared by Michael Fordis and the NIH Office of Education. A special thanks to the Office for Research on Women's Health and the Office of Equal Employment Opportunity for their suggestions. ■

Honoraria Ban Continues

On March 30, 1993, the U. S. Court of Appeals for the District of Columbia Circuit issued its decision in the "honoraria" case, *National Treasury Employees Union* v. *United States*. The decision upheld the judgment of the District Court that the honoraria ban violates the First Amendment rights of executive branch employees.

The original District Court decision in this case, which also held that the statute was unconstitutional, stayed its judgment pending appeal. For this reason the honoraria ban continued in effect. Subsequently, on May 14, the Department of Justice (DOJ) announced its intentions to appeal the Court of Appeals decision; therefore, despite the Court of Appeals' decision to strike it down, the honoraria ban will remain in effect, at least until a decision is made on the DOJ appeal.

While the honoraria ban continues, employees may not receive compensation for certain articles, speeches, and appearances. However, employees are reminded that compensation prohibited by the ban may be placed in escrow or donated to a qualified charitable organization. ■

FAX-BACK

In this issue, we are asking for your opinion on the recommendations made by the Task Force on the Status of Women Scientists, on technology transfer at NIH, and on the NIH Campus master plans. In addition, we have three questions on the technology, resources and services provided by NCRR. The center will use this feedback to draft its own strategic plan. Fax your comments to 402-4303 or mail it to us at Bldg 1, Room 134.

1) What do you think about the recommendations made by the Task Force on the Status of Women Scientists at NIH?

2) What aspects of the tech-transfer process would you like to see improved?

3) Which NIH Campus would you choose—The Park or The Quad?

4) Which NCRR technologies, resources, and services are vital to your present research? How well do they meet your current needs? Use separate page and respond by July 15.

5) What are the most important basic and clinical research trends in your area of interest that will drive your future research efforts? Which research technologies, resources and services will be critical to facilitate this research and why? Use separate page and respond by July 15.

6) Whom would you recommend to serve as a panel member for NCRR's strategic planning process? Please list name, address, phone number, and specific area of expertise. Use separate page and respond by July 15.

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Editor
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Deputy Director for Intramural Research, OD

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Copyeditor
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Photography
Robert Cooke

U.S. Department of
Health and Human Services
Public Health Service
National Institutes of Health
Building 1, Room 134
Bethesda, Maryland 20892